ABSTRACT

Of the dissertation for the degree of Doctor of Philosophy Ph.D. in the specialty 8D07105 "Chemical technology of organic substances" Amankulova Dinara Erkinovna on the topic "Development of a method for non-catalytic synthesis of *meta*-aryloxyphenols from 1,3-cyclogexanedione"

General description of work. The focus of this project is to develop a method for the non-catalytic synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione. The goal is on establishing a simple and efficient process for producing *meta*-substituted phenols using readily available starting materials.

Relevance of the research topic. *Meta*-(aryloxy)phenols have been widely studied for their efficient and versatile chemical properties. They serve as useful synthetic intermediates for the synthesis of natural and biologically active compounds such as pharmaceuticals, agrochemicals, and dyes. Additionally, *meta*-(aryloxy)phenols exhibit exceptional antioxidant, antimicrobial, and anti-inflammatory activities, which make them potential candidates for a broad range of industrial and medicinal applications.

Moreover, the *meta*-substituted nature of these phenols further enhances their efficiency by conferring unique steric and electronic properties that can be optimized for specific applications. This attribute enables the development of highly selective and efficient catalysts, ligands, and chiral auxiliaries that are employed in numerous chemical processes, including asymmetric synthesis, cross-coupling reactions, and polymerization.

The synthesis of *meta*-(aryloxy)phenols has been a long-standing challenge in organic chemistry due to the complex nature of the reaction and the difficulties associated with achieving high yields and selectivity. Traditional synthetic methods involve the use of transition metal catalysts, which can be expensive and often require rigorous reaction conditions that can lead to undesired byproducts and low yields. Additionally, the use of transition metals can pose environmental concerns, and the presence of metal residues in the final product may limit their applications in various industries, including pharmaceuticals and materials science.

Furthermore, the steric and electronic properties of *meta*-substituted phenols are highly dependent on the specific substituents present, which can make the synthesis of these compounds even more difficult. Achieving precise control over the position and nature of the substituents can be difficult, and small changes in reaction conditions can lead to significant changes in product distribution and properties.

Despite these challenges, the development of efficient and practical methods for the synthesis of *meta*-(aryloxy)phenols is of great importance due to their diverse range of applications, including their use as synthetic intermediates and in medicinal

and industrial applications. As such, continued efforts are being made to develop more efficient and environmentally friendly methods for their synthesis, which will allow for their wider use in various fields of chemistry.

The degree of development of the problem. The current state of research on the synthesis of *meta*-(aryloxy)phenols has shown significant progress. While various methods have been developed to synthesize these compounds, the non-catalytic approach is of particular interest due to its potential for industrial-scale production and reduced cost. Recent studies have focused on optimizing reaction conditions and improving yields, as well as exploring the versatility of the resulting compounds in various applications.

Despite the progress made in the field, there is still room for further development of efficient and practical methods for the non-catalytic synthesis of *meta*-(aryloxy)phenols. Future research may focus on the use of alternative reaction conditions and reagents to improve yields and selectivity, as well as the development of new synthetic routes to access more complex and diverse structures.

The purpose of the dissertation research. The objective of the present dissertation research is to develop an efficient and novel method for the synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione.

To accomplish this goal, the following tasks were undertaken:

- formation of 3-chlorocyclohex-2-en-1-one from cyclohexan-1,3-dione by utilizing the Vilsmeier reagent;
- conduction of research on the conditions of obtaining 3-(aryloxy)cyclohex-2-en-1-one by nucleophilic substitution reaction;
- introduction of a directing group by C(2) bromination of 3-(aryloxy)cyclohex-2-en-1-one;
- conduction of research on the conditions of synthesis of *meta*-(aryloxy)phenols by oxidative aromatization;
- structure analysis of synthesized compounds through various techniques such as IR spectroscopy, mass spectrometry, and NMR spectroscopy;
- representation technological schemes for the developed methods for the synthesis of intermediate and final compounds and calculate the material balance of production.

The main provisions of the dissertation submitted for defense:

1. A novel approach for synthesizing *meta*-(aryloxy)phenols via cyclohexane-1,3-dione has been devised, comprising a four-step synthesis protocol. The method has yielded eight *meta*-(aryloxy)phenols in high quantities, with an average yield of 66% for all eight compounds.
2. The method avoids the need for operations to bypass the *ortho-, para-* directing effect of oxygen, resulting in a simplified and streamlined synthesis process. The

required 1,3-functional group relationship is inherent in the readily available cyclohexane-1,3-dione starting material, allowing for easy access to the desired *meta*-(aryloxy)phenols.

3. The synthesis method does not entail the use of heavy metals or ligands, rendering it a more ecologically sound and safer substitute to conventional techniques.

The objects of study in this dissertation research are cyclohexane-1,3-dione and its derivatives, as well as various reagents and conditions for the synthesis of *meta*-(aryloxy)phenols.

The subject of the study is the development of a new and efficient method for the synthesis of *meta*-(aryloxy)phenols from cyclohexane-1,3-dione.

The dissertation was carried out aligning with the priorities of scientific development, as approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan. Specifically, it pertained to scientific research in the field of natural sciences.

Research methods - mass spectrometry, IR spectroscopy, ^{1}H, ^{13}C NMR spectroscopy.

The scientific novelty of the work.

- A new and efficient method for the non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione in four steps. All steps don'trequired high temperature and don't involve any heavy metals or ligandswere developed.
- The method has been successfully utilized to synthesize eight distinct *meta*-aryloxy phenols, four of which have not been previously documented in the literature. Additionally, the method has yielded 16 intermediate products, 14 of which have not been previously reported in literature.
- The chemical structures of newly synthesized compounds have been characterized for the first time using a combination of analytical techniques.

Theoretical and practical significance. The theoretical significance of the developed method lies in the discovery of a new and efficient approach for the synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione. This approach offers a unique alternative to the conventional methods that involve the use of heavy metals or ligands and require additional steps to bypass the *ortho-, para-* directing effect of oxygen.

The practical significance of this method lies in its potential for industrial applications, as it offers a cost-effective and environmentally friendly approach to the synthesis of *meta*-(aryloxy)phenols. These compounds have a wide range of applications in various fields, including pharmaceuticals, agrochemicals, and dyes, as well as in the development of highly selective and efficient catalysts, ligands, and chiral auxiliaries used in various chemical processes. The developed method can also be used as a platform for the synthesis of novel *meta*-substituted phenolic compounds with tailored steric and electronic properties, which can be optimized for specific industrial and medicinal applications.

Compliance with priority areas of science development or government programs. The dissertation was carried out aligning with the priorities of scientific development, as approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan. Specifically, it pertained to scientific research in the field of natural sciences.

The author's personal contribution. The author made a significant contribution to the development and implementation of experiments, the solution of theoretical and practical problems, and the interpretation of the results. She collaborated with researchers in the Dr. Clive group laboratory at the University of Alberta.

She also played a key role in the preparation and writing of a review article published in the journal "Molecules". Furthermore, the author synthesized 24 out of the 51 compounds discussed in an article published in the journal "Tetrahedron".

Approbation of work. Main provisions and results of the dissertation presented and discussed at international conference: the «Фараби Әлемі – 2023» conference for students and young scientists in 2023.

Publications. During the course of the research conducted for this dissertation, three scientific papers were published. Including the article in the Q2-ranked journal Tetrahedron (with a 60% percentile) and another article in the Q2-ranked journal Molecules (with an 83% percentile). Additionally, the findings of this research have been presented and discussed in international conference, such as the «Фараби Әлемі – 2023» conference for students and young scientists in 2023.

The structure and scope of the dissertation. The dissertation is presented as 115 pages of typewritten text and includes abbreviations, an introduction, a literature review, a discussion of results, an experimental part, conclusions and a list of sources used from 128 items, and an appendix for 50 pages. The dissertation work contains 75 schemes, 5 figures and 25 tables.